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Principles of Drug Therapy in Patients with Renal Disease

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Patients with reduced renal function commonly require drug therapy for various associated conditions. Most drugs are fully or partially excreted by the kidney; therefore, drug dosage regimens often need to be adjusted in order to provide safe yet effective treatment for patients with renal disease. In addition, certain therapeutic agents have potential nephrotoxicity and pharmacologic actions that may jeopardize already compromised renal function. Understanding of drug pharmacology, the therapeutic dose and the speed of drug elimination in a given patient will lead to correct assessment of the drug regimen.

WIDESPREAD AVAILABILITY of facilities to care for patients with chronic renal disease has notably increased the numbers and types of patients presenting themselves to physicians for long-term medical management. Coexisting diseases and age no longer present insurmountable obstacles to application of dialysis and transplantation. Coincident with this trend has been a proliferation of newer and more potent therapeutic agents available for treatment. Most drugs are fully or partially excreted by the kidney; therefore, drug dosage regimens often need to be adjusted in order to provide safe yet effective treatment for patients with renal insufficiency. In addition, the altered biochemical milieu imposed by chronic renal disease may lead to adverse effects with many common drugs. Indeed, certain therapeutic agents have potential nephrotoxicity and pharmacologic actions that can jeopardize already compromised renal function. The present communication will present a theoretical basis for renal failure dosage adjustments and some practical guidelines for constructing these therapeutic regimens. The subsequent discussion has as its basis the general principle that correct assessment of a drug regimen requires knowledge of the pharmacology of the drug, the therapeutic dose and the speed of elimination in a given patient.

The basic factors and determinants of any drug's pharmacologic effect are absorption, distribution in body fluids and drug elimination. A schematic representation of these drug pharmacokinetic processes is shown in Figure 1. These factors as they relate to a patient with renal disease will be handled separately in the following sections.

Drug Absorption from the Gastrointestinal Tract and from Intramuscular Injection Sites

When a drug is in solution, some important determinants of its absorption are the character of the membranes it must cross to reach the circulation, blood flow at the absorption site, surface

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ABBREVIATIONS USED IN TEXT

C = concentration of the drug in the blood
Cl_{Cr} = creatine clearance
C_0 = concentration in the blood at zero time assuming instant mixing
D_L = loading dose
GFR = glomerular filtration rate
K% = the overall rate constant for elimination of the drug from the body as a percent per hour
pKa = the pH at which the drug is in equilibrium between the ionized and un-ionized state
t½ = half-life
V_D = volume of distribution
X_B = amount of drug in the body

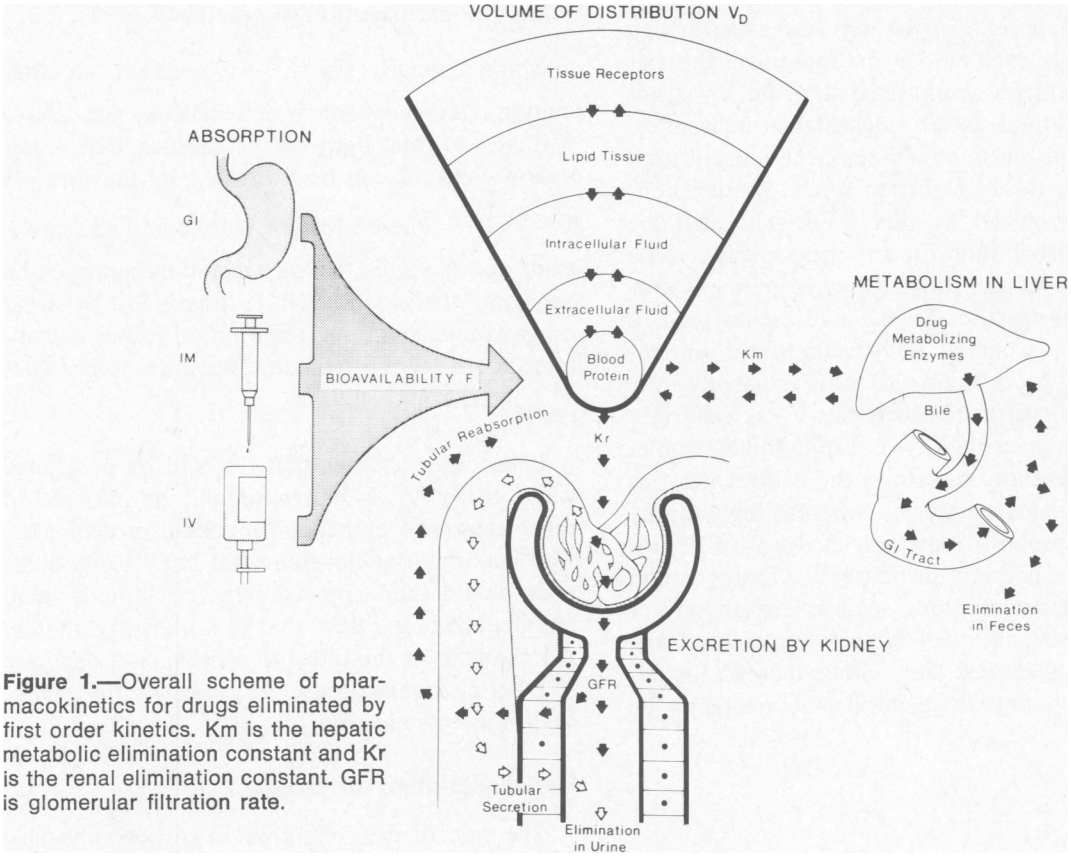

Figure 1.—Overall scheme of pharmacokinetics for drugs eliminated by first order kinetics. Km is the hepatic metabolic elimination constant and Kr is the renal elimination constant. GFR is glomerular filtration rate.

area available for absorption and contact time between drug and absorption surface. The physiochemical properties of the drug, such as lipid solubility, pKa and molecular size, are obviously also critical. Little is known specifically about variability in drug absorption in human renal failure, but certainly the gastrointestinal disturbances in renal failure (nausea, vomiting, diarrhea and gastrointestinal tract edema) could alter absorption. In addition, many drugs may add to gastrointestinal symptoms experienced by uremic patients by either local irritative or other pharmacologic actions. Edematous patients in general absorb drugs more slowly from intramuscular injection sites.

Drug Distribution

Each drug distributes through the body in a characteristic manner. The apparent volume of distribution (V_D) is given by dividing the amount of drug in the body (X_B) by the concentration of the drug in the blood (C), or $V_D = \frac{X_B}{C}$. This volume of distribution can be simply estimated by plotting drug concentration versus time on semilogarithmic paper as is shown in Figure 2. Extrapolation of the straight portion of the log-linear curve back to zero time yields the value for C_0, the concentration in the blood at zero time assuming instant mixing. Since instant mixing does not usually occur, this value is only at best an esti-

mate. By dividing C_0 into the administered dose adjusted for the percent absorbed, the apparent volume of distribution is obtained.

Once V_D has been derived for a drug, it may be used to calculate the amount of drug remaining in the body when the plasma concentration is known and falls on the exponential portion of the decay curve; or, conversely, it may be used to predict the initial blood level—that is, C_0—following a given dose. (For example, for gentamicin, $V_D = 15$ liters. An 80 mg dose should then give a blood level of 5.3 micrograms (μg) per ml.) It should be emphasized that the V_D is not necessarily equal to an identifiable anatomical compartment, but is a mathematical concept used to relate the dose of a drug to the plasma concentration achieved by that dose. Although the volume of distribution for any drug seems to be a characteristic of the drug, this measurement may be altered by disease. Edema and ascites tend to increase V_D, whereas dehydration and upright posture tend to decrease it.[1] This is usually only of clinical importance when the V_D is relatively small (such as <50 liters). Lipid soluble molecules preferentially penetrate the central nervous system and have a large V_D, whereas high affinity for plasma proteins may restrict drugs to the intravascular space and decrease V_D. Drugs bound tightly to tissue receptors, such as digitalis glycosides, tend to have very large volumes of distribution. Renal disease may either increase or decrease V_D so that no general statement can be made.

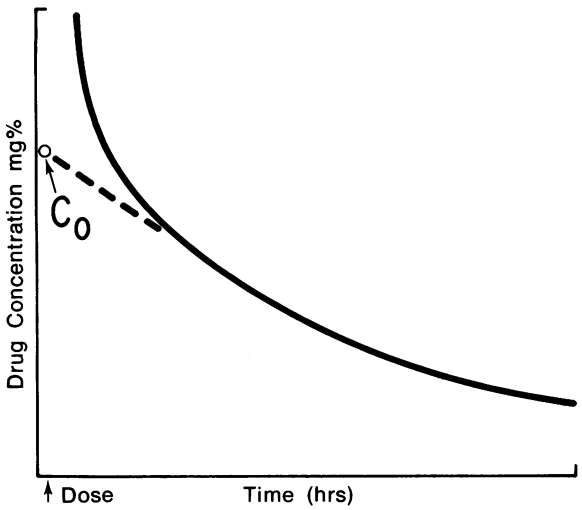

Figure 2.—Theoretical log-linear plot of drug concentration in blood against time for a drug eliminated by first order kinetics. C0 is the concentration achieved at zero time assuming complete and instant mixing.

Drug Elimination

Most drugs are eliminated from the body by first order kinetics, that is, the amount of drug eliminated from the body in a unit of time is proportional to the amount of drug in the body at that time. The rate of drug removal is usually expressed by its half-life ($t\frac{1}{2}$). Factors which modify this rate include the volume of distribution, renal function, extent of tissue binding, lipid solubility and hepatic drug metabolism.

Mathematically, $t\frac{1}{2} = \frac{.693}{K}$ where K is an elimination rate constant which reflects the above variables of total body drug clearance. The elimination constant can be expressed by the formula $K = \frac{k_r + k_m}{V_D}$ where k_r is the renal elimination constant and k_m is the hepatic metabolic elimination constant.[2] This assumes little drug is lost by sweat or gastrointestinal secretion. If one then substitutes for K in the half-time formula, it becomes $t\frac{1}{2} = \frac{.693 \times V_D}{k_r + k_m}$.

It becomes obvious that $t\frac{1}{2}$ will be prolonged when either V_D is increased and/or the rate of renal clearance or hepatic metabolism decreases. The maximum achievable total body drug clearance would then approximate the sum of renal and hepatic blood flow, that is, 3 liters per minute. An example of the effect of incremental decrease in renal clearance on the $t\frac{1}{2}$ is shown in Table 1, for a theoretical drug.

Renal Handling of Drugs

The rate of drug elimination through the glomerulus depends on the glomerular filtration rate, the concentration of drug in the blood and the proportion that is bound to plasma proteins. Tubular reabsorption of the drug may occur, and tends to be rather complete with lipid soluble compounds. Many pharmacologic agents are

TABLE 1.—*The Effect of the Decrease in Renal Clearance on Drug Half-life*

V_D (liters)	Renal drug clearance (ml/min)	$t\frac{1}{2}$ (min)
15	700	15
15	100	104
15	50	208
15	10	1,020
15	2	5,220

V_D = volume of distribution
$t\frac{1}{2}$ = half-life

weak acids or weak bases, and are transported from the peritubular blood into the urine by various tubular secretory mechanisms. Secretion of these compounds tends to be influenced by other drugs competing for transport sites. An example is the diminution of methotrexate excretion by salicylate and other organic anions. Some common drugs that use the weak acid secretory system for elimination are the thiazide diuretics, sulfonamides, penicillins, probenecid and methotrexate.

Other drugs that are weak acids or bases may have their excretion modified by luminal pH. This depends on the pKa of the compound, which is the pH at which the drug is in equilibrium between the ionized and un-ionized state. At low urine pH, weak acids with low pKa tend to be more un-ionized and thus more easily reabsorbed, whereas if urine pH is increased, ionization and urinary excretion are enhanced. Table 2 includes some agents whose excretion is modified by urinary pH.

In general, manipulation of urinary pH by alkalinization or acidification is successful in enhancing excretion of drugs when the drug is normally excreted by the kidney rather than metabolized by the liver, or if metabolic pathways are saturated by large quantities of drug. Other helpful factors include a pKa in the range of achievable urinary pH (5.0 to 8.0), and greater water than lipid solubility.

Drug Metabolism or Biotransformation

Many drugs are metabolized to inactive compounds before excretion. These processes usually take place in the endoplasmic reticulum of hepatic cells under the influence of drug metabolizing enzymes. These enzymes may oxidize, reduce, hydrolyze or conjugate drugs to more polar compounds which are then pharmacologically inactive, water soluble and more easily excreted in the urine. In general, oxidation of drugs is normal in renal failure[3] or may even be accelerated. The latter has been described for diphenylhydantoin, although decreased protein binding and higher "free" levels may contribute to increased removal.[4] Few drugs undergo reduction reactions; however, the reduction of hydrocortisone has been shown to be decreased in renal failure.[5] Glucuronidation is normal in uremia, while many acetylation reactions are slowed. It becomes obvious that knowledge of any given drug's metabolic fate is necessary to predict metabolic alterations produced by renal failure. Some metabolic transformations of common drugs and the effects of uremia are listed in Table 3.

TABLE 2.—*Drugs with Excretion Enhanced by Altering Luminal pH*

Enhanced excretion in alkaline urine (pH>7)	*Enhanced excretion in acid urine (pH<5)*
Acetazolamide	Amitryptyline
Phenobarbital	Amphetamine
Phenylbutazone	Imipramine
Sulfonamides	Meperidine
Salicyclic acid	Quinine
	Quinidine
	Chloroquin

Increased Sensitivity to Drugs

Reduced plasma protein binding of drugs in renal failure (such as barbiturates, narcotics and diphenylhydantoin) will increase the unbound or free fraction of the blood concentration of drug. Enhanced and prolonged pharmacologic effects may result.[6] In addition, the blood-brain barrier may be altered in uremia, promoting increased drug uptake within the central nervous system. Care must be taken in prescribing drugs with decreased plasma protein binding to uremic patients, especially those with low serum proteins.

Altering Dosage in Renal Failure

When patients receive multiple dose regimens at uniform dose intervals, the average plasma concentration accumulates until a steady state concentration is reached. Under such circumstances, the time required to reach approximately 90 percent of the steady state drug concentration is 3.3 times the t½. Since the t½ may be greatly prolonged in renal failure, effective therapy may be greatly delayed if maintenance dosage is given adjusted to the renal failure t½. Therefore, a loading dose is usually necessary to achieve acceptable initial therapeutic effectiveness. This principle is particularly applicable when planning antibiotic and digitalis therapy. For practical purposes, the usual initial drug dosage is not changed unless the drug in question has a narrow toxic-therapeutic ratio or there is an altered V_D (as in edema or obesity). Most studies which consider alteration of drug regimens in renal failure have involved antibiotics. Adjustment of dosage is usually dictated by the prolongation of t½ which is, in turn, estimated by the degree of reduction in glomerular filtration rate. Since the usual clinical determinations of serum creatinine or creatinine clearance do not

TABLE 3.—*Effects of Uremia on Metabolism of Common Drugs (Adapted from Reidenberg[7])*

Metabolic Process	*Drug*	*Effect of Uremia*
Oxidation	Acetohexamide	? slowed
	Dephenylhydantoin	Drug metabolite induces increased oxidation
	Phenacetin	None
	Phenobarbital	None
	Quinidine	None
	Tolbutamide	None
Reduction	Hydrocortisone	Slowed
Ester hydrolysis	Procaine	Slowed
Tissue peptide degradation	Insulin	Slowed, probably due to lack of renal metabolism
Glucuronidation	Chloramphenicol	None
	Indomethacin	None
	Tyroxine	None
	Triiodothyronine	None
Acetylation	Hydralazine	Slowed in some people*—genetically determined slow acetylators
	Isoniazid	Slowed in genetically determined slow acetylators*; normal in fast acetylators
	Paraamino salicylic acid	Slowed
	Sulfonamides	Slowed

*True also of a normal population.

reflect true glomerular filtration rate or overall renal function (such as tubular mechanisms), these recommended adjustments are only first approximations at best. Increasing use of available serum drug concentrations should improve therapy.[7]

These levels can be interpreted fully only if the elapsed time from the last dose and the t½ in that particular patient are known. To obtain the best estimate of the peak blood concentration, blood should be sampled one to two hours after an oral dose and one hour after an intravenous or intramuscular dose. Caution must be exercised when interpreting results from drugs which have altered drug-protein binding in uremia since free and pharmacologically active levels may be increased despite normal total drug levels. Likewise, when metabolic processes produce pharmacologically active metabolites (such as azathioprine and propranolol) normal or low serum levels of the original drug may be misleading.

Various strategies can be used when devising dosage schedules in renal failure. The most commonly used methods are the constant dose-varying interval method and the reduced dose-constant interval method. The former is simple to apply but produces peaks and valleys in serum levels of drug while the latter produces more constant blood levels but necessitates fractions of usual dosages. Some drugs lend themselves to constant intravenous infusions, and although therapy can be precisely adjusted, the complexity and monitoring required make routine use impractical. A new method, proposed by Orr and co-workers,[8] employing the occupancy principle which involves calculating the time during which a drug resides in a certain body space, has not yet attained wide acceptance. The use of these strategies is illustrated in the following sections describing techniques for administering various commonly used pharmacologic agents to patients with renal failure.

Antimicrobial Therapy

The basic goal of antibiotic therapy is to achieve a steady state blood and tissue level which is both effective and nontoxic. Ideally, the steady state concentration will oscillate with time so that the lowest concentration would exceed the minimum value necessary to kill the organism in question, and the peak concentration is below the level which gives side effects or toxicity. Since with antibiotic therapy the patient is most ill when the drug is first given, a loading dose should be administered. Therefore, a usual or even slightly increased initial dose should be given to ill patients with renal failure.

To adjust maintenance therapy for renal failure, one of several approaches can be used. Dettli and co-workers[2] and Wagner[9] have suggested the following approach which requires knowledge concerning the relationship between the overall rate constant for elimination of the drug from the body as a percent per hour (K%)

and the creatinine clearance (Cl_{Cr}). This is shown in Figure 3. Mathematically, $K\% = a + b\ Cl_{Cr}$, where K% is the overall elimination rate constant, a is the portion of elimination rate constant due to nonrenal losses, and b Cl_{Cr} is the portion of the elimination rate constant due to renal losses of the drug. Graphically, a is the intercept on the y axis of K% plotted versus Cl_{Cr}, and b is the slope.

To calculate the elimination t½ for any given value of K% in renal failure, use the formula $t½ = \frac{69.3}{K\%}$. To make dosage adjustment for renal impairment, use the equation $D_r = D_m \times \frac{\text{patient } K\%}{\text{normal } K\%}$, where D_r is the dose in renal failure and D_m is the usual maintenance dose.

In order to plan gentamicin therapy for a 70-kg patient with renal failure and a Cl_{Cr} of 10 ml per minute, a normal volume of distribution the same as extracellular fluid (15 liters) and a desired peak blood level of 10 μg per ml are assumed. Since the loading dose (D_L) is not altered in renal failure, it can be calculated by rearranging the formula $V_D = \frac{D_L}{C}$, to $D_L = V_D \times C$. $D_L = 15$ liters $\times 10$ μg per ml, which gives a result of $D_L = 150$ mg or 2.1 mg per kg. Maintenance doses can be calculated as illustrated below. Values for the constants a and b are obtained from a data table, and normal creatinine clearance is assumed to be 100 ml per minute. Using the overall formula $K\% = a + b\ Cl_{Cr}$, the normal K% for gentamicin

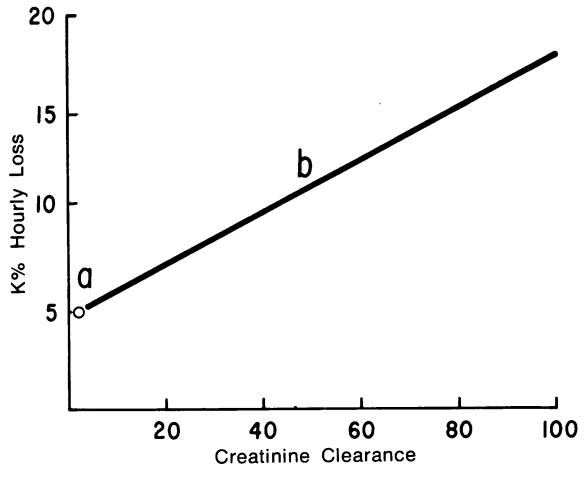

Figure 3.—Relationship of the overall elimination constant K% expressed as hourly percent loss and creatinine clearance. The a is percent hourly loss due to nonrenal processes and b is slope of the line.

is equal to $2 + .28 \times 100$ ml per minute. It then follows that $K\% = 2 + 28$, or $K\% = 30$. The K% in the theoretical patient is equal to $2 + .28 \times 10$ ml per minute, or 4.8. Thus, the maintenance dose for our patient is equal to 70 (the usual maintenance of 1 mg per kg for a 70-kg person) times 4.8 (the K% for the theoretical patient), divided by 30 (the normal K%). Calculating through, the new maintenance dose is equal to $70 \times \frac{4.8}{30}$, or 11 mg. This 11 mg can be given at the usual dosage time interval of eight hours. Data for the appropriate constants as derived from the literature[7,8] are compiled in Table 4. The t½ in the theoretical patient would be $\frac{69.3}{4.8}$, or approximately 14.5 hours.

Simpler methods have evolved for the commonly used aminoglycoside antibiotics using the t½. These drugs are usually excreted unchanged in the urine and have little metabolic transformation. The t½ can be related to the glomerular filtration rate (GFR) and serum creatinine in such a way that a 50 percent loss of renal function results in a doubling of the t½.[10]

For kanamycin, the t½ in hours equals three times serum creatinine. Normal dosage interval is 12 hours (every third t½, since normal t½ is four hours). Therapeutic serum level is 10 to 30 μg per ml, and a loading dose of 7 mg per kg of

TABLE 4.—*Elimination Constants and Slopes for Various Antibiotics (Adapted from Dettli et al[2] and Wagner[9])*

Drug	*a*	*b*	*Normal K%*	*Normal t½*
Ampicillin	11.0	.59	70	1.0
Carbenicillin	6.0	.54	60	1.2
Cephalexin	3.0	.67	70	1.0
Cephalothin	6.0	1.34	140	.5
Chloramphenicol	20.0	.10	30	2.3
Colistin	8.0	.23	31	2.2
Doxycycline	3.0	0	3	23.0
Erythromycin	13.0	.37	50	1.4
5-fluorocytosine	.7	.24	25	2.8
Gentamicin	2.0	.28	30	2.3
Kanamycin	1.0	.24	25	2.75
Lincomycin	6.0	.09	15	4.6
Methicillin	17.0	1.23	140	.5
Oxacillin	35.0	1.05	140	.5
Penicillin G	3.0	1.37	140	.5
Streptomycin	1.0	.26	27	2.6
Sulfamethoxasole	7.0	0	7	9.9
Tetracycline	.8	.07	8	8.7
Trimethoprim	2.0	.04	6	12.0
Vancomycin	.3	.12	12	5.8

a = percent hourly loss due to nonrenal processes
b = slope of the line
K% = the overall rate constant for elimination of the drug from the body as a percent per hour
t½ = half-life

body weight will achieve a peak level within this range. Since t½ is serum creatinine times three, and the dose is given every third t½, the dosage interval in renal failure is nine times serum creatinine.[11] Serum creatinine must be stable to apply this formula—that is, dosage for a 70-kg man with serum creatinine of 3.0 would be calculated as 7×70, or 490 mg every 27 hours (3×9). Since 50 percent of dose is removed by dialysis, 3.5 mg per kg of body weight should be supplemented after the average dialysis.

For gentamicin, the t½ in hours equals four times serum creatinine. Normal dosage interval is eight hours—every third t½. (The usual interval of eight hours probably results in drug levels which are subtherapeutic for considerable times, and the drug would more properly be given every four hours or every six hours.) Therapeutic serum level is 4 to 10 μg per ml, and a loading dose of 2 to 3 mg per kg will achieve a peak level in this range. Since t½ is serum creatinine times four, and one should give the drug every second t½, the dosage interval in renal failure should be the serum creatinine times eight[12] (that is, a 70-kg man with serum creatinine of 3.0 would get 140 mg [2×70] every [3×8] 24 hours). Since 75 to 100 percent of dose is removed by dialysis, 1 mg per kg of body weight should be supplemented after the average dialysis.

Because of the considerable interval during which subtherapeutic concentrations of drug exist using fixed interval therapy,[13] a compromise approach might be 2 to 3 mg per kg load and 1 mg per kg every t½; or the method which we prefer, 2 mg per kg and .4 mg per kg at intervals of two times the serum creatinine in hours. Blood levels should be used to monitor therapy one hour after a dose for peak levels (should be <12 μg per ml) or before the next dose for trough levels (should be >2 μg per ml). In critically ill patients, gentamicin can be given by continuous intravenous infusion.[14] The infusion rate in mg per minute is equal to ten times serum level desired divided by the t½ in minutes.

For antibiotic drugs where less than 15 percent of the drug appears unchanged in the urine, no dosage modification for renal failure is necessary.[13] Examples of these would include lincomycin, clindamycin, isoniazid and doxycycline. Chloromycetin is not primarily handled by renal excretion, although antibacterially inactive metabolites are renally excreted. These metabolites may cause marrow toxicity when they accumulate.

Some antibiotic drugs with major renal excretion do not need dosage modification because, although blood levels may increase notably, the results of such increase are usually clinically insignificant.[14] These in general include penicillins, cephalosporins and sulfonamides. Extremely high drug levels of penicillins may cause coagulopathy and hypokalemic metabolic alkalosis and seizures in patients with renal failure.[15-17] Cephaloridine, unlike other cephalosporins, causes nephrotoxic reactions in doses greater than 4 grams per day. These are manifested as proximal tubular necrosis and the drug should be carefully adjusted in patients with renal disease.

Some antibiotics should be avoided in renal failure.[18] A nitrofurantoin metabolite can accumulate and cause peripheral neuritis if the GFR is less than 20 ml per minute. The tetracycline group, except doxycycline, are antianabolic agents and therefore promote azotemia and acidosis.

Cardiac Glycosides

For cardiac glycosides it is customary to reduce the dosage and give the drug at the usual daily dosage interval. Jelliffe[19] computed the t½ of digoxin in subjects with normal renal function and found it to be 1.6 days. Therefore, in the usual 24-hour dosing interval 35 percent of the total amount of drug in the body was lost. Patients who were anuric had t½ of 4.4 days and lost 14 percent of their digoxin stores per day. The 14 percent presumably represents extrarenal metabolism. If the total body stores are known (V_D), then the daily maintenance dose should be 14 percent of the stores or loading dose, plus an additional percentage of body stores to replace urinary losses. The daily urinary losses are proportional to the creatinine clearance. Since about 20 percent of the body's digoxin stores are lost daily by renal excretion at a creatinine clearance of 100 ml per minute, approximately 10 percent will be lost if the clearance is 50 ml per minute, 5 percent if the clearance is 25 ml per minute and so forth. This percentage added to the 14 percent nonrenal losses should give the correct maintenance dose. If the digitalizing dose is not known, the body stores can be estimated from the serum digoxin level and the V_D which is 7.3 liters per kg of lean body weight by the formula $7.3 \text{ (weight in kg)} = \frac{\text{body stores}}{\text{serum level}}$.[20] For digitalizing patients with renal failure, most clinicians

give the usual or only slightly reduced loading doses of digoxin.[21] It should be noted that with a change in the maintenance dose a new steady state is not reached for approximately four times t½. Digoxin is not appreciably dialyzed clinically.

Digitoxin is mainly eliminated from the body by nonrenal routes. Renal failure therefore has much less effect in altering digitoxin kinetics.[22] The t½ in patients with normal renal function is six days, which corresponds to a daily percent loss of 11 percent of body stores. An anuric patient has a t½ of 8.5 days and loses 8 percent of body stores daily. It is of interest that about 8 percent of daily digitoxin losses are due to conversion to digoxin by the liver. Thus, digitoxin dosage schedules, although theoretically needing minor alterations in renal failure, need not be too different from usual therapy. The maintenance dose for renal failure expressed as percentage of usual dose is 63 percent for anuric patients, 79 percent if Cl_{Cr} is 50 ml per minute and 86 percent if Cl_{Cr} is 75 ml per minute.[22]

Drug-Drug Interactions

Clinically, the problem of therapy in renal disease is complicated by the necessity for multiple therapy and possible drug-drug interactions. These can result in enzyme inductions or inhibitions in hepatic drug metabolizing enzymes. Drugs may displace other drugs from receptors at sites of action decreasing the effect of the displaced drug, or, conversely, drugs may displace other drugs from plasma proteins increasing pharmacologic action of the displaced drug. Finally, one drug may influence the renal excretion or intestinal absorption of another agent. A discussion of drug interactions in renal disease has been published recently.[23]

Dialysis of Drugs and Poisons

Generalizations can be made regarding the potential value of dialysis in the management of poisoning or need to adjust dosage for loss of therapeutic efficacy due to dialysis losses. First, the drug should diffuse through dialysis membrane in significant amounts. Second, a significant quantity of substance should be in plasma water and thus presumably accessible for diffusion. Finally, to be useful in poisoning, toxic effects should relate to plasma concentration and duration of the drug in body, and the amount dialyzed should be a significant addition to amount of drug elimination by other means.

A list of drugs where dialysis may be useful for poisonings is shown in Table 5.

Drugs which should be supplemented to replace dialysis losses and general guidelines for therapy with common drugs in patients with renal insufficiency are available in several recent references.[18,24,25]

TABLE 5.—*Well-established Indications for Dialysis of Overdoses*

Drug	*Indication*
Methyl alcohol	Blood level >50 mg per 100 ml
Ethyl alcohol	Blood level >300 mg per 100 ml
Phenobarbital	Blood level >20 mg per 100 ml
Carbon tetrachloride.	Within 1st 48 hours after ingestion
Ethylene glycol	Within 1st 48 hours after ingestion
Aspirin	Blood level >90 mg per 100 ml

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